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Ambient Water Quality Criteria for Diphenylhydrazine

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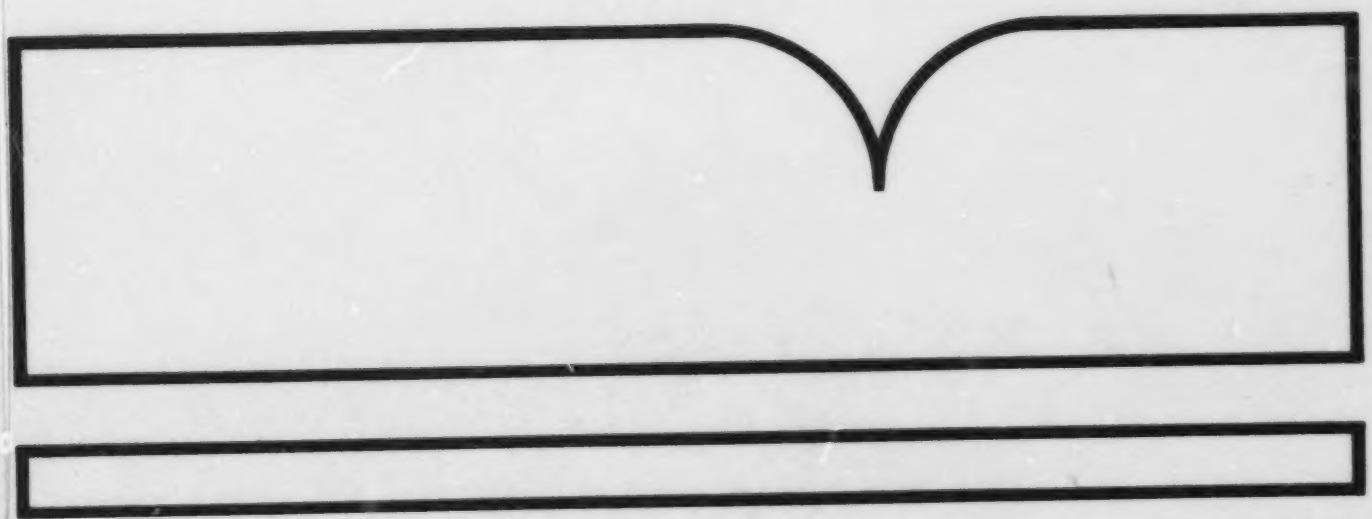

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Ambient Water Quality Criteria for Diphenylhydrazine

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16. ABSTRACT
Section 304(A) of the Clean Water Act [33 U.S.C. 1314(A)], requires EPA to publish and periodically update water quality criteria. These criteria are to reflect the latest scientific knowledge on the identifiable effects of pollutants on public health and welfare, aquatic life, and recreation. This report presents water quality criteria for Diphenylhydrazine. It presents concentration criteria for the protection of freshwater and saltwater aquatic life. It presents 'safe' concentrations for humans, and in the case of suspect or proven carcinogens, gives various levels of incremental cancer risk. A Section 304(A) water quality criterion is a qualitative or quantitative estimate of the concentration of a water constituent or pollutant in ambient waters which, when not exceeded, will ensure a water quality sufficient to protect a specified water use. Under the Act a criterion is a scientific entity, based solely on data and scientific judgment. It does not reflect considerations of economic or technological feasibility nor is it a water quality standard and in itself has no regulatory effect.

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AMBIENT WATER QUALITY CRITERIA FOR

DIPHENYLHYDRAZINE

Prepared By
U.S. ENVIRONMENTAL PROTECTION AGENCY

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FOREWORD

Section 304 (a)(1) of the Clean Water Act of 1977 (P.L. 95-217), requires the Administrator of the Environmental Protection Agency to publish criteria for water quality accurately reflecting the latest scientific knowledge on the kind and extent of all identifiable effects on health and welfare which may be expected from the presence of pollutants in any body of water, including ground water. Proposed water quality criteria for the 65 toxic pollutants listed under section 307 (a)(1) of the Clean Water Act were developed and a notice of their availability was published for public comment on March 15, 1979 (44 FR 15926), July 25, 1979 (44 FR 43660), and October 1, 1979 (44 FR 56628). This document is a revision of those proposed criteria based upon a consideration of comments received from other Federal Agencies, State agencies, special interest groups, and individual scientists. The criteria contained in this document replace any previously published EPA criteria for the 65 pollutants. This criterion document is also published in satisifaction of paragraph 11 of the Settlement Agreement in Natural Resources Defense Council, et. al. vs. Train, 8 ERC 2120 (D.D.C. 1976), modified, 12 ERC 1833 (D.D.C. 1979).

The term "water quality criteria" is used in two sections of the Clean Water Act, section 304 (a)(1) and section 303 (c)(2). The term has a different program impact in each section. In section 304, the term represents a non-regulatory, scientific assessment of ecological effects. The criteria presented in this publication are such scientific assessments. Such water quality criteria associated with specific stream uses when adopted as State water quality standards under section 303 become enforceable maximum acceptable levels of a pollutant in ambient waters. The water quality criteria adopted in the State water quality standards could have the same numerical limits as the criteria developed under section 304. However, in many situations States may want to adjust water quality criteria developed under section 304 to reflect local environmental conditions and human exposure patterns before incorporation into water quality standards. It is not until their adoption as part of the State water quality standards that the criteria become regulatory.

Guidelines to assist the States in the modification of criteria presented in this document, in the development of water quality standards, and in other water-related programs of this Agency, are being developed by EPA.

STEVEN SCHATZOW
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CRITERIA DOCUMENT

DIPHENYLHYDRAZINE

CRITERIA

Aquatic Life

The available data for 1,2-diphenylhydrazine indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 270 ug/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of 1,2-diphenylhadrazine to sensitive freshwater aquatic life.

No saltwater organisms have been tested with 1,2-diphenylhydrazine and no statement can be made concerning acute or chronic toxicity.

Human Health

For the maximum protection of human health from the potential carcinogenic effects due to exposure of diphenylhydrazine through ingestion of contaminated water and contaminated aquatic organisms, the ambient water concentrations should be zero based on the non-threshold assumption for this chemical. However, zero level may not be attainable at the present time. Therefore, the levels which may result in incremental increase of cancer risk over the lifetime are estimated at 10^{-5}, 10^{-6}, and 10^{-7}. The corresponding recommended criteria are 422 ng/l, 42 ng/l, and 4 ng/l, respectively. If the above estimates are made for consumption of aquatic organisms only, excluding consumption of water, the levels are 5.6 ug/l, 0.56 ug/l, and 0.056 ug/l, respectively.

INTRODUCTION

Diphenylhydrazine exists as an asymmetrical isomer, 1,1-diphenylhydrazine, and a symmetrical isomer, 1,2-diphenylhydrazine (hydrazobenzene). The hydrochloride of 1,1-diphenylhydrazine is used as a reagent for the sugars, arabinose and lactose (Windholz, 1976). 1,2-Diphenylhydrazine is used in the synthesis of phenylbutazone (Wenner, 1967) and as the starting material in the manufacture of benzidine, an intermediate in the production of dyes (Lurie, 1964).

The primary method of commercial production of this compound is the reduction of nitrobenzene by catalysts such as Fe^{+3} or Zn^{+2} in alkaline solution. By this procedure, nearly quantitative yields are obtained (Kirk-Othmer, 1963). Figure 1 depicts this process as well as the by-products of diphenylhydrazine, azobenzene and azoxybenzene.

In 1977 the commercial production of 1,2-diphenylhydrazine was in excess of 1,000 lbs. [Stanford Research Institute (SRI), 1977]. However, this figure is probably an underestimate of the amount of diphenylhydrazine that was actually available. Diphenylhydrazine is produced in several synthetic processes as an intermediate or as a contaminant, but it is not possible to estimate these quantities, which are probably substantial.

The reaction of 1,2-diphenylhydrazine with acid results in the benzidine rearrangement (Kenner, 1968). This reaction is presented in Figure 2. In addition to benzidine, other products formed include diphenyline, o-benzidine, and o-semidine. In the stomach, 1,2-diphenylhydrazine can be converted into benzidine, a known human carcinogen [Haley, 1975; International Agency for Research on Cancer (IARC), 1972].

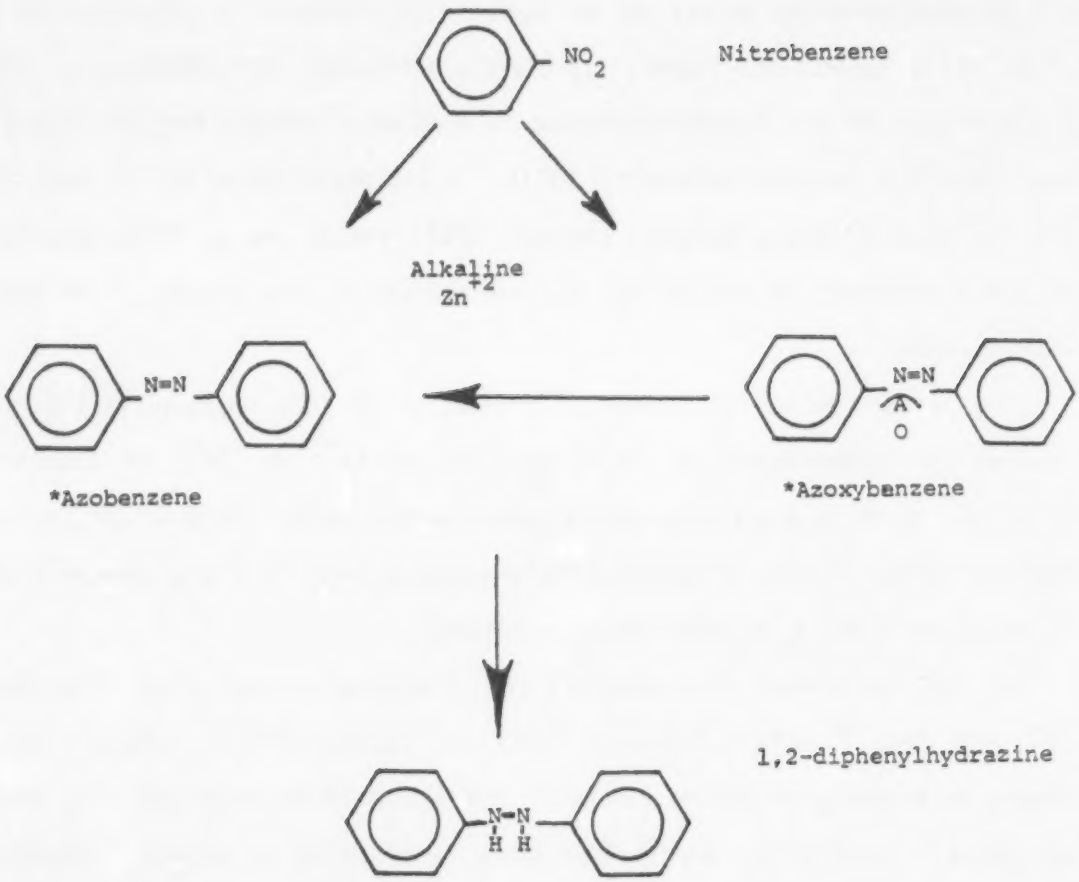


FIGURE 1

Synthesis of 1, 2-diphenylhydrazine

Source: Williams, 1959

*Carcinogenic

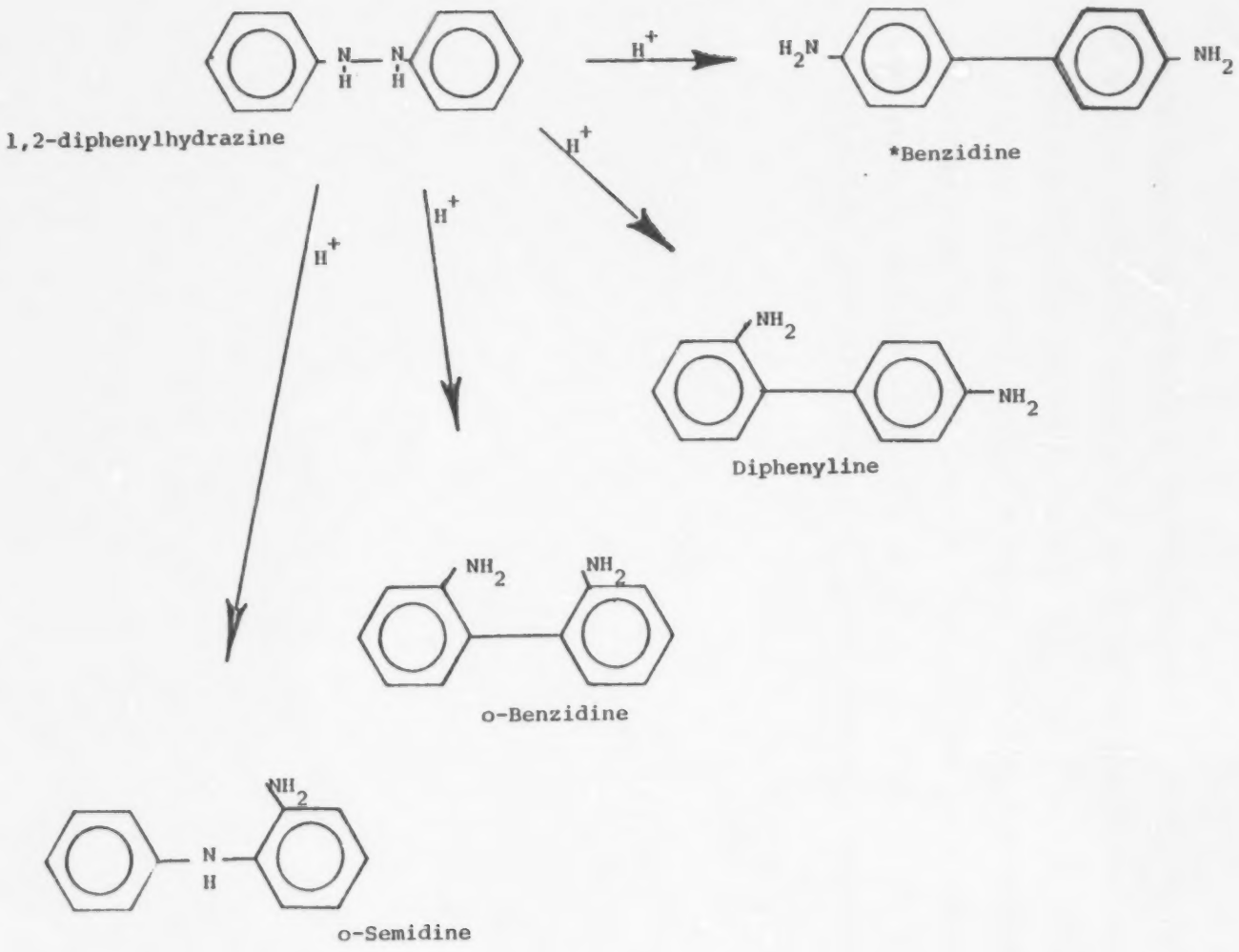


FIGURE 2

Benzidine Rearrangement of 1, 2-diphenylhydrazine

Source: Williams, 1959

*Carcinogenic

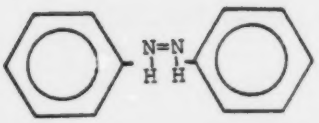
The structure and physical data for 1,2-diphenylhydrazine are presented in Figure 3.

No data were found on the environmental presence or persistence of diphenylhydrazines, except for one report of detection in drinking water at a concentration of 1 ug/l (U.S. EPA, 1975). 1,1-Diphenylhydrazine and 1,2-diphenylhydrazine have been characterized as slightly soluble and insoluble in water, respectively (Windholz, 1976; Bennett, 1974). No quantitative data were found for the water solubilities and vapor pressures of these compounds; consequently, no predictions can be made about their persistence in water.

FIGURE 3

1,2-diphenylhydrazine: Chemical and Physical Properties

Source: Weast, 1978.



Synonyms - Hydrazobenzene

Symmetrical diphenylhydrazine

N, N'-Diphenylhydrazine

N, N'-Bianiline

1,1' -Hydrazodibenzene

Cas No. 530-50-7

Molecular weight = 184.24

Melting Point = 131°C

Boiling Point = 220°C

Solubility = Slightly soluble in water

Very soluble in benzene, ether, alcohol

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Aquatic Life Toxicology*

INTRODUCTION

Toxicity tests with 1,2-diphenylhydrazine and the bluegill and Daphnia magna have been conducted using static procedures, and the results demonstrated adverse effects as low as 270 µg/l. No data are available for any saltwater species.

EFFECTS

Acute Toxicity

The 48-hour EC_{50} for Daphnia magna and the 96-hour LC_{50} for the bluegill are 4,100 µg/l and 270 µg/l, respectively, for 1,2-diphenylhydrazine (Table 1).

Summary

Only two freshwater species have been tested with 1,2-diphenylhydrazine. The range of 50 percent effect levels for the bluegill and Daphnia magna was 270 to 4,100 µg/l. No data are available for 1,2-diphenylhydrazine and saltwater organisms.

CRITERIA

The available data for 1,2-diphenylhydrazine indicate that acute toxicity to freshwater aquatic life occurs at concentrations as low as 270 µg/l and would occur at lower concentrations among species that are more sensitive than those tested. No data are available concerning the chronic toxicity of 1,2-diphenylhydrazine to sensitive freshwater aquatic life.

No saltwater organisms have been tested with 1,2-diphenylhydrazine and no statement can be made concerning acute or chronic toxicity.

*The reader is referred to the Guidelines for Deriving Water Quality Criteria for the Protection of Aquatic Life and Its Uses in order to better understand the following discussion and recommendation. The following tables contain the appropriate data that were found in the literature, and at the bottom of each table are calculations for deriving various measures of toxicity as described in the guidelines.

Table 1. Acute values for 1,2-diphenylhydrazine (U.S. EPA, 1978)

Species	Method[a]	LC50/EC50 (µg/l)	Species Acute Value (µg/l)
	FRESHWATER SPECIES		
Cladoceran, *Daphnia magna*	S, U	4,100	4,100
Bluegill, *Lepomis macrochirus*	S, U	270	270

[a] S = static, U = unmeasured

No Final Acute Values are calculable since the minimum data base requirements are not met.

REFERENCES

U.S. EPA. 1978. In-depth studies on health and environmental impacts of selected water pollutants. U.S. Environ. Prot. Agency, Contract No. 68-01-4646.

Mammalian Toxicology and Human Health Effects

EXPOSURE

Ingestion from Water

1,2-Diphenylhydrazine (DPH) was not detected in the finished water of any of 10 cities selected for a detailed study by U.S. EPA (1975). However, the same study demonstrated the presence of DPH in drinking water in concentrations up to 1 µg/l (1 ppb).

Ingestion from Food

There are no available data identifying DPH as a direct or indirect food additive, or as a naturally occurring constituent of any food.

A bioconcentration factor (BCF) relates the concentration of a chemical in aquatic animals to the concentration in the water in which they live. The steady-state BCFs for a lipid-soluble compound in the tissues of various aquatic animals seem to be proportional to the percent lipid in the tissue. Thus, the per capita ingestion of a lipid-soluble chemical can be estimated from the per capita consumption of fish and shellfish, the weighted average percent lipids of consumed fish and shellfish, and a steady-state BCF for the chemical.

Data from a recent survey on fish and shellfish consumption in the United States were analyzed by SRI International (U.S. EPA, 1980). These data were used to estimate that the per capita consumption of freshwater and estuarine fish and shellfish in the United States is 6.5 g/day (Stephan, 1980). In addition, these data were used with data on the fat content of the edible portion of

the same species to estimate that the weighted average percent lipids for consumed freshwater and estuarine fish and shellfish is 3.0 percent.

No measured steady-state bioconcentration factor (BCF) is available for 1,2-diphenylhydrazine, but the equation "Log BCF = (0.85 Log P) - 0.70" can be used (Veith, et al. 1979) to estimate the BCF for aquatic organisms that contain about 7.6 percent lipids (Veith, 1980) from the octanol/water partition coefficient (P). Based on a measured log P value of 2.94 (Hansch and Leo, 1979), the steady-state bioconcentration factor for 1,2-diphenylhydrazine is estimated to be 63. An adjustment factor of 3.0/7.6 = 0.395 can be used to adjust the estimated BCF from the 7.6 percent lipids on which the equation is based to the 3.0 percent lipids that is the weighted average for consumed fish and shellfish. Thus, the weighted average bioconcentration factor for 1,2-diphenylhydrazine and the edible portion of all aquatic organisms consumed by Americans is calculated to be 63 x 0.395 = 24.9.

Inhalation, Dermal, and Other Sources

Laboratory workers, workers in forensic medicine, and workers involved in the manufacture of dyes, certain pharmaceuticals, and chemicals, are subject to occupational exposure to 1,2-diphenylhydrazine. Both inhalation and dermal contact are possible routes of exposure in these settings. However, no experimental data are available to quantitate either the dermal or inhalation exposure risks to this population.

PHARMACOKINETICS

Absorption, Excretion, and Distribution

There is little available data on the absorption or excretion of 1,2-diphenylhydrazine by mammals. The administration of DPH by various routes results in systemic effects and the presence of DPH metabolites in the urine, indicating some degree of absorption.

Metabolism

The metabolism of 1,2-diphenylhydrazine in the rat is presented in Figure 1 (Williams, 1959). The compound was administered to rats orally (p.o.) (200, 400 mg/kg), intraperitoneally (i.p.) (200 mg/kg), intratracheally (5, 10 mg/kg), and intravenously (i.v.) (4, 8 mg/kg). Urine was analyzed chromatographically (TLC) and the metabolic scheme shown in Figure 1 was proposed. Benzidine was identified as a metabolite. The metabolites detected were not dependent upon the dose or the route of administration.

EFFECTS

Acute, Subacute, and Chronic Toxicity

Two studies reporting oral LD_{50} values for DPH were identified. Marhold, et al. (1968) used 10 male Wistar rats and administered DPH as a 5 percent aqueous suspension. The LD_{50} value was reported to be 959 mg/kg. Liver damage is an important feature of diphenylhydrazine toxicity, particularly after chronic exposure. Sutton (1967) noted that phenylhydrazines cause prominent kidney damage and more diffuse liver damage in animals.

No epidemiological studies of DPH exposure have been conducted.

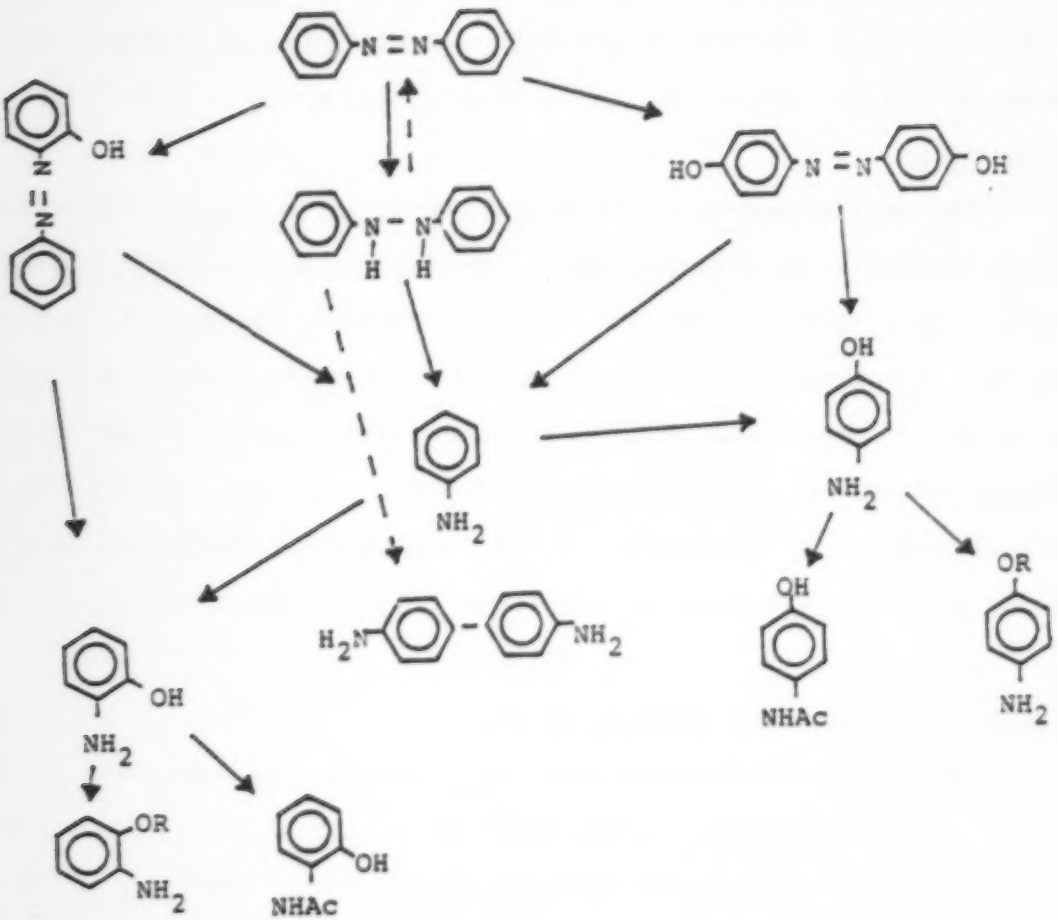

FIGURE 1

1,2-Diphenylhydrazine Metabolites in Rat Urine
Source: Williams, 1959

Synergism and/or Antagonism

Marhold, et al. (1968) demonstrated that diphenyline, a product of benzidine rearrangement, acts synergistically with benzidine to produce tumors. Genin (1975) showed synergism of hydrazobenzene with benzidine sulfate. Kurlyandskii, et al. (1976) observed that benzidine sulfate-hydrazobenzene or benzidine sulfate-dianisidine sulfate mixtures when administered subcutaneously to rats increased the incidence of bladder cancer and decreased the latent period for tumor development when compared with the carcinogenic activity of the individual compounds. The authors emphasized the importance of preventing the possible exposure of industrial workers to combinations of 1,2-diphenylhydrazine and benzidine during the manufacture of benzidine sulfate.

Teratogenicity

Pertinent data could not be located in the available literature on the teratogenicity of DPH.

Mutagenicity

Sieler (1977) studied the incorporation of ^{3}H-thymidine into testicular DNA using the technique developed by Friedman and Staub (1976). When DPH was administered i.p. in a dose of 100 mg/kg, an inhibitory effect on testicular DNA synthesis was observed. In this study, a limited number of structurally related compounds were assayed. The relationship between the known mutagenicity of some of these agents agreed favorably with effects on depressed testicular DNA synthesis. These authors then concluded that agents which can depress testicular DNA synthesis may have a mutagenic potential.

Carcinogenicity

Concern over 1,2-diphenylhydrazine is based on several factors: (1) its presence in drinking water (at concentrations up to 1 µg/l (U.S. EPA, 1975); (2) the likely production of benzidine from DPH in the stomach due to gastric acidity [International Agency for Research on Cancer (IARC), 1972]; (3) the documented carcinogenicity of diphenylhydrazine and selected substituted hydrazines (IARC, 1974); (4) the increased incidence of bladder cancer among workers involved in the manufacture of dyes (Wynder, et al. 1963; Anthony, et al. 1970); (5) the carcinogenicity of azobenzene, a metabolite of DPH, as well as the established carcinogenicity of benzidine to which DPH is converted.

There are several reports on the possible carcinogenicity of DPH. In a study by the National Cancer Institute (NCI, 1978), technical grade DPH* was fed as a dietary admixture to Fischer 344 rats and mice ($B_6C_3F_1$) of both sexes. Dietary concentrations of DPH fed to rats and mice are indicated in Tables 1 and 2. In this study, DPH was fed to mice and rats for 78 weeks followed by observation periods of 17 to 96 weeks and 28 to 109 weeks, respectively. Controls consisted of 47 to 50 animals of each sex. The results of this study are summarized in Tables 1 and 2. There were differences in the nature and organ distribution of tumors between sexes and species. DPH was carcinogenic to Fischer 344 rats of both sexes and caused significant increases in hepatocellular carcinoma

*mp = 120 - 124°C (K & K labs)

TABLE 1

Carcinogenicity of 1,2-Diphenylhydrazine in $B6C3F_1$ Mice*

Sex	#	Dose[a]	Weeks		Effects	
			Treated	Observed Post Treatment	Hepatocellular Carcinomas	Pulmonary Carcinomas
Male	50	LD control	0	95	12/50	5/50
	50	HD control	0	96	6/48	5/49
	50	0.008	78	17	11/47	1/47
	50	0.040	78	17	8/46	0/46
Female	50	LD control	0	96	2/47	2/46
	50	HD control	0	96	1/50	3/50
	47	0.004	78	17	4/39	3/38
	50	0.040	78	18	20/43 $p < 0.001$	2/40

*Source: NCI, 1978.
[a]Dose = % DPH in diet.
LD = Low dose.
HD = High dose.

TABLE 2

Carcinogenicity of 1,2-Diphenylhydrazine in Fischer 344 Rats*

Sex		Dose[a]	Weeks		Effects		
			Treated	Observed	Hepatocellular Carcinomas or Neoplastic Nodules	Zymbal's Gland Squamous Cell Carcinomas	Other Tumors
							Adrenal Tumors
Male	50	LD control	0	108	5/47	0/47	7/47
	49	HD control	0	109	1/48	0/48	8/47
	50	0.008	78	29	13/49 $p = 0.040$	1/50	7/48
	50	0.03	78	28	37/49 $p < 0.001$	5/49 $p = 0.030$	16/46 $p < 0.001$
							Mammary Carcinomas
Female	50	LD control	0	109	0/47	0/48	1/48
	50	HD control	0	109	0/50	0/50	0/50
	50	0.004	78	30	0/50	1/50	3/50
	50	0.010	78	29	6/50 $p < 0.013$	0/50	6/50 $p = 0.013$

*Source: NCI, 1978.
[a]Dose = % DPH in diet.
LD = Low dose.
HD = High dose.

or neoplastic nodules in male rats at both doses; Zymbal's gland squamous-cells or adrenal tumors in male rats at the high dose; and neoplastic liver nodules or mammary carcinomas in female rats at the high dose. Female mice showed an increase in hepatocelluar carcinomas only at the high dose. DPH was not carcinogenic in $B6C3F_1$ male mice.

In a study by Pliss (1974), the carcinogenic properties of DPH were studied over a period of 588 days in rats (N = 163) and C57 mice (N = 110). DPH was suspended in sunflower seed oil and administered by subcutaneous (s.c.) injection (40 mg/wk/rat and 5 mg/wk/mouse), and by addition to food (30 mg/5 times/wk) or application to the skin (2 mg/3 times/wk/mouse).

The data summarized in Table 3 indicate that DPH produces a wide variety of tumors in both mice and rats.

In contrast to the studies of NCI (1978) and Pliss (1974), Marhold, et al. (1968) and Spitz (1950) did not find DPH to be carcinogenic. The latter two studies were difficult to interpret due to the lack of specific information on the purity of DPH, experimental design, or statistical analysis. The Pliss study (1974) should be used in a cautious manner in indicting DPH as a carcinogen. The author indicated that animals had to be added to the study in order to replace animals afflicted with a parasitic infection. In addition, although the tumor incidence was given for DPH-treated animals, the incidence of tumors in control animals was not presented except in the case of the epicutaneous administration of DPH. Values of 17 percent vs. 22.2 percent for control and DPH

TABLE 3

Carcinogenicity of DPH in Mice and Rats*

Species	Route	Effects	
		% Tumor Incidence	Tumors
Mice	s.c.	36.6	Rhabdomyosarcoma
	p.o.	50	Pulmonary adenoma, leukemia, liver
	epicutaneous	22.2	Skin, lung, liver
Rats	s.c.	22.6	Uterus, mammary, Zymbal's gland, liver, spleen, lymphoid leukemia

*Source: Pliss, 1974.

groups, respectively, were presented but no statistical analysis of these incidences was given. In light of the available information, the NCI data indicates that DPH is carcinogenic.

CRITERION FORMULATION

Existing Guidelines and Standards

Existing guidelines or standards were not found for 1,2-diphenylhydrazine.

Current Levels of Exposure

Pertinent data could not be located in the available literature on the concentration of 1,2-diphenylhydrazine in the atmosphere.

1,2-Diphenylhydrazine has been found to be present in drinking water at levels of 1 µg/l = 1 ppb (U.S. EPA, 1975).

1,2-Diphenylhydrazine has not been found to be a natural constituent of food.

Special Groups at Risk

Manufacturers of dyes and pharmaceuticals are subject to occupational exposure. Groups working in the laboratory and forensic medicine may also be subject to 1,2-diphenylhydrazine exposure.

Basis and Derivation of Criterion

An evaluation of the subacute, acute and chronic toxicity, with the exception of carcinogenicity is impossible because of scanty data. Guidelines or standards presently do not exist for DPH. Diphenylhydrazine has been shown to produce carcinogenic responses in rats and mice (NCI, 1978; Pliss, 1974). Since the NCI (1978) study represents the only report in which all the data can be analyzed, it will be used as a basis for formulating a criterion.

Under the Consent Decree in NRDC v. Train, criteria are to state "recommended maximum permissible concentrations (including

where appropriate, zero) consistent with the protection of aquatic organisms, human health, and recreational activities." DPH is suspected of being a human carcinogen. Because there is no recognized safe concentration for human carcinogens, the recommended concentration of DPH in water for maximum protection of human health is zero.

Because attaining a zero concentration level may be infeasible in some cases and in order to assist the Agency and states in the possible future development of water quality regulations, the concentrations of DPH corresponding to several incremental lifetime cancer risk levels have been estimated. A cancer risk level provides an estimate of the additional incidence of cancer that may be expected in an exposed population. A risk of 10^{-5} for example, indicates a probability of one additional case of cancer for every 100,000 people exposed, a risk of 10^{-6} indicates one additional case of cancer for every million people exposed, and so forth.

In the Federal Register notice of availability of draft ambient water quality criteria, EPA stated that it is considering setting criteria at an interim target risk level of 10^{-5}, 10^{-6}, or 10^{-7} as shown in the following information.

Exposure Assumptions	Risk Levels and Corresponding Criteria (1)			
	0	10^{-7}	10^{-6}	10^{-5}
2 liters of drinking water and consumption of 6.5 g fish and shellfish (2)	0	4 ng/l	42 ng/l	422 ng/l
Consumption of fish and shellfish only	0	56 ng/l	560 ng/l	5,600 ng/l

(1) Calculated by applying a linearized multistage model as discussed in the Human Health Methodology Appendices to the October 1980 Federal Register notice which announced the availability of this document. Appropriate bioassay data used in the calculation of the model are presented in the Appendix. Since the extrapolation model is linear to low doses, the additional lifetime risk is directly proportional to the water concentration. Therefore, water concentrations corresponding to other risk levels can be derived by multiplying or dividing one of the risk levels and corresponding water concentrations shown in the table by factors such as 10, 100, 1,000 and so forth.

(2) Seven percent of the DPH exposure results from the consumption of aquatic organisms which exhibit an average bioconcentration potential of 24.9-fold. The remaining 93 percent of DPH exposure results from drinking water.

Concentration levels were derived assuming a lifetime exposure to various amounts of DPH, (1) occurring from the consumption of both drinking water and aquatic life grown in water containing the corresponding DPH concentrations and, (2) occurring solely from consumption of aquatic life grown in the waters containing the corresponding DPH concentrations.

Although a total exposure evaluation for DPH is desirable there is no data to support a total exposure analysis. The criteria presented, therefore, assume an incremental risk from assumed ambient water exposure only.

For DPH the case for criterion development is based upon the existence of carcinogenicity responses in animals (rats and mice).

Because of the lack of investigations for other chronic and acute responses, no information on other effects exists in either human or animal systems. Thus, the criterion proposed should be considered as precautionary until further studies can be used in the overall toxicity evaluations.

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APPENDIX

Summary and Conclusions Regarding the Carcinogenicity of 1,2,-Diphenylhydrazine*

1,2-Diphenylhydrazine is used primarily in dye manufacturing industries as a precursor in the synthesis of benzidine. There are no data showing carcinogenic effects of 1,2-diphenylhydrazine in humans. However, two studies have shown that 1,2-diphenylhydrazine is carcinogenic in mice and rats via subcutaneous and oral routes of administration. Male rats, receiving dietary concentrations of 0.03 percent 1,2-diphenylhydrazine, developed hepatocellular carcinomas, squamous cell carcinomas of the Zymbal's gland, and adrenal tumors. Female rats, receiving 0.01 percent 1,2-diphenylhydrazine in the diet, developed neoplastic nodules of the liver and mammary adenocarcinomas. Female mice, exposed to 0.04 percent 1,2-diphenylhydrazine in the diet, developed hepatocellular carcinomas.

The carcinogenic responses induced in male and female rats and female mice constitute substantial evidence that 1,2-diphenylhydrazine is likely to be a human carcinogen.

The water quality criterion for 1,2-diphenylhydrazine is based on the induction of hepatocellular carcinoma and neoplastic nodules in male Fischer 344 rats, exposed to a time-weighted average concentration of 0.008 or 0.03 percent (80 or 300 ppm) 1,2-diphenylhydrazine in the diet for 78 weeks (NCI, 1978). The concentration of 1,2-diphenylhydrazine in water calculated to keep the lifetime cancer risk below 10^{-5} is 0.42 µg/l.

*This summary has been prepared and approved by the Carcinogens Assessment Group of EPA on June 15, 1979.

Summary of Pertinent Data

The water quality criterion for 1,2-diphenylhydrazine is based on the induction of hepatocellular carcinomas and neoplastic nodules in male Fischer 344 rats, exposed to various concentrations of 1,2-diphenylhydrazine in the diet ad libitum for 78 weeks (NCI, 1978). The criterion was calculated from the following parameters:

Dose (mg/kg/day)	Incidence (no. responding/no. tested)
0	6/95
4	13/49
15	37/49

le = 78 weeks
Le = 104 weeks
L = 104 weeks

w = 0.380 kg
R = 24.9 l/kg

With these parameters the carcinogenic potency for humans, q_1^*, is 0.768 $(mg/kg/day)^{-1}$. The resulting water concentration of 1,2-diphenylhydrazine, calculated to keep the individual lifetime cancer risk below 10^{-5}, is 0.42 µg/l.